RCOphth Essay Prize.
Artificial Intelligence (AI) in retinopathy of prematurity screening in middle-income countries

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Background

- It is estimated that 20,000 infants have blindness or severe visual impairment due to retinopathy of prematurity (ROP).[i]
- Middle-income countries are currently experiencing a surge in ROP incidence - the "**third epidemic**".
  - Explained by improvements in neonatal care coupled with unregulated supplementary oxygen use.[ii,iii,iv]
- Issues in middle income countries include a lack of implemented widespread screening programmes, with a paucity of ophthalmologists and infrastructure to screen and treat ROP appropriately.[ii,iii,iv,v]
  - E.g., in Guatemala there are 474 babies eligible for screening for every ophthalmologist partaking in the screening programme.[v]
- Screening inclusion criteria is comparable to high-income countries therefore does not reflect the at-risk cohort. Different demographics are affected by ROP – specifically less premature and larger babies.[ii]

Deep learning

- AI application in ROP screening is based on deep learning algorithms interpreting fundus images.
- Deep learning is an algorithm based on developing pattern recognition capabilities from a raw teaching data set.[vi]
- A trial assessing a deep learning algorithm (i-ROP DL) versus experts in the diagnosis of plus disease using posterior retinal images showed sensitivity and specificity of 93% and 94% respectively.[vii]
- Average accuracy was deemed higher than 6/8 experts.[vii]
- Misclassifications made by the algorithm did not result in mislabelling plus disease as normal or vice-versa.[vii]

Screening

AI in screening provides opportunities to meet unmet demands especially where there is a low ratio of specialist ophthalmologists to eligible babies.

There have been four reported ways to integrate AI into screening.[x]

1. Use AI exclusively[x]
   a. Set thresholds would result in many false-positives leading to significant costs due to unnecessarily examining patients – not fulfilling AI's objectives.[x]
2. Initial screening is performed by AI, subsequently all positive-screens are reviewed - reducing the burden on human resources.[x]
3. Initial screening by AI with subsequent review of all positives and a subset of negative-screens.[i] Thus allowing for adaptive learning of AI algorithms whilst evaluating safety through false-negative identification, reducing the cost of labour but also the potential benefits of AI.[x]
4. AI algorithm is used alongside a humans in telemedicine.[x] This allows for a period of AI assessment in the real-world, allowing rigorous safety testing and a difference-in-difference study to determine any significant impact on patient care.[x]

Telemedicine

- Extensively used in some middle income-countries such as Chile and India.[viii,ii,vii]
- In Chile, screening is established in all regions with 39% of neonatal intensive care units using telemedicine.[viii,ix]
- Telemedicine is used for follow-up allowing image comparison to determine disease progression.[viii]
- There was a 98% concordance between treatment threshold disease on imaging and indirect ophthalmoscopy.[viii]
- Screening via telemedicine may decrease the time burden on ROP ophthalmologists, reducing costs, helping meet unmet demand.[iv,xi]
- AI would be a further extension to help expand screening in resource restricted settings.

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Challenges

- Without real-world evidence and a known incidence of diagnostic errors, AI cannot ethically be used to provide fully automated diagnoses.[x]
- It is imperative to understand how the algorithm reached its conclusion to ensure outcomes are based on known clinically relevant pathological findings - this requires studies to explain and troubleshoot areas that require more data input.[x]
- AI is a fragile system which can be significantly impacted by changes imperceptible to humans - so-called erratic behaviour.[x]
- Application is only valid in highly-specific predefined circumstances therefore other abnormalities would not be detected.[x]

Accountability

- When an error occurs due to AI there is an innate difficulty in providing an explanation due to the nebulous nature of neural networks.[x]
  - There is no clear way of creating additional safeguards to prevent their reoccurrence.x[i]

Conclusion

- In resource-limited settings AI could be transformative in the delivery of care as it has the possibility to overcome challenges such as a lack of access to expert care, or to assist in situations where demand cannot be met with the current traditional infrastructure.[x]
- In some cases, it may be a comparison between AI and no diagnosis at all.[x] This research question is not the same as non-inferiority, or clinical benefit trials designed for high-income countries. Therefore, further research is warranted into interventions designed for middle income countries.
- ROP diagnoses have significant variability between ophthalmologists. Interpretation of AI outputs could assist in reducing variability through education and insight into cognitive processes.[ii,iv]
- Whilst AI may play a role in the future of ROP screening, automated diagnosis algorithms are not available for mainstream use. A recent systematic review described AI in ROP as currently only having a role as a clinical adjuvant.[xi]
- Integrating AI and telemedicine would potentially allow for larger scale role outs of ROP screening worldwide.